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ORIGINAL ARTICLE

Pharmacogenomics study of thiazide diuretics and QT interval in multi-ethnic populations: the cohorts for heart and aging research in genomic epidemiology

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Thiazide diuretics, commonly used antihypertensives, may cause QT interval (QT) prolongation, a risk factor for highly fatal and difficult to predict ventricular arrhythmias. We examined whether common single-nucleotide polymorphisms (SNPs) modified the association between thiazide use and QT or its component parts (QRS interval, JT interval) by performing ancestry-specific, trans-ethnic and cross-phenotype genome-wide analyses of European (66%), African American (15%) and Hispanic (19%) populations ($N = 78\,199$), leveraging longitudinal data, incorporating corrected standard errors to account for underestimation of interaction estimate variances and evaluating evidence for pathway enrichment. Although no loci achieved genome-wide significance ($P < 5 \times 10^{-8}$), we found suggestive evidence ($P < 5 \times 10^{-6}$) for SNPs modifying the thiazide-QT association at 22 loci, including ion transport loci (for example, *NELL1, KCNQ3*). The biologic plausibility of our suggestive results and simulations demonstrating modest power to detect interaction effects at genome-wide significant levels indicate that larger studies and innovative statistical methods are warranted in future efforts evaluating thiazide–SNP interactions.

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INTRODUCTION

Over the past decade, the use of prescription drugs has skyrocketed, with nearly half of all Americans now taking at least one prescription drug.[1] Accompanying the increased prevalence of drug use is a high burden of adverse drug reactions (ADRs), which account for approximately 100 000 deaths and 2.2 million serious health effects annually.[2–4] QT interval (QT) prolongation, which can trigger fatal ventricular arrhythmias, is a long-recognized adverse effect[5] of numerous common medications, such as antipsychotics, antibiotics, antiarrhythmics and antihypertensives.[6] Within the past ten years, QT prolongation has represented the most common cause for withdrawal of a drug from the market (or relabeling) after approval by the US Food and Drug Administration (FDA).[7,8] However, drug-induced QT prolongation remains difficult to predict.[9]

Genetic variants are known to mediate both pharmacokinetic and pharmacodynamic processes, thereby playing a major role in drug response.[10] Pharmacogenomics, which evaluates the role of genetics in drug response, offers a promising avenue for understanding variation in drug response,[11] illuminating novel pathways, informing drug development and selection,[12–14] optimizing dosing regimens[15–19] and avoiding ADRs.[20–22] QT is highly heritable (35–40%).[23–27] Previous pharmacogenomics studies of drugs associated with QT prolongation, including thiazide diuretics, a common anti-hypertensive therapy used by over a quarter of the United States hypertensive population,[28] identified multiple loci associated with anti-hypertensive response and ADRs.[29–34] Furthermore, thiazide diuretics are used unequally across race/ethnic groups in the United States, with approximately 10% of Hispanic/Latinos, 13% of European Americans, and 23% of African Americans taking a thiazide diuretic.[28,35,36] Therefore, the pharmacogenomics of thiazide-induced QT prolongation represents an excellent but understudied candidate for pharmacogenomic inquiry.

We previously examined evidence for common single-nucleotide polymorphisms (SNPs) that modified the association between thiazide use and QT and failed to identify any genome-wide significant loci ($P < 5 \times 10^{-8}$).[37] However, our previous study was limited to European descent populations and cross-sectional analyses, despite many of the contributing studies having longitudinal drug and electrocardiographic data.[37] Here, we expand upon that work, applying recent statistical innovations to leverage longitudinal data and including an additional 44 418 participants of European, African American, and Hispanic/Latino descent to perform the first trans-ethnic genome-wide association study (GWAS) to examine genetic associations that modify the association between thiazides and QT, as well as the component parts of QT (JT interval (JT), QRS interval (QRS)).

MATERIALS AND METHODS

Study populations

Fourteen cohorts from in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)[38] Pharmacogenomics Working Group (PWG) participated in this analysis, contributing 78 199 participants: European descent (51 601), African American (11 482), and Hispanic/Latino (15 116) participants (Table 1; Supplementary Text). Among the fourteen cohorts, six (55% of the total population) had repeated measurements of medication use and electrocardiogram (ECG) assessments and contributed longitudinal data to the analysis: Age, Gene/Environment Susceptibility—Reykjavik Study (AGES), Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Health Study (CHS), Rotterdam Study (RS), Multi-Ethnic Study of Atherosclerosis (MESA), and Women's Health Initiative (WHI). The remaining eight cohorts contributed cross-sectional data to the analysis: Framingham Heart Study (FHS), Erasmus Rucphen Family (ERF) Study, Health 2000 (H2000), Health, Aging, and Body Composition (Health ABC), Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), Jackson Heart Study (JHS), Netherlands Epidemiology of Obesity (NEO) Study, and Hispanic Community Health Study/Study of Latinos (HCHS/SOL).

Study design

Participants with ECG measurements, medication assessment, and genome-wide genotype data were eligible for inclusion. The following exclusion criteria were applied: poor ECG quality, atrial fibrillation detected by ECG, pacemaker implantation, second or third degree atrioventricular heart block, QRS greater than 120 ms, prevalent heart failure, pregnancy, missing ECG, missing medication assessment, missing genotype information, or race/ethnicity other than European descent, African American, or Hispanic/Latino. For studies with longitudinal data, exclusion criteria were applied on a visit-specific basis.

Medication assessment

Medication use was assessed through medication inventories conducted during clinic visits, home interviews, or through pharmacy databases (Supplementary Table 1). Six studies captured medication used on the day of the study visit. A further six of the 14 participating cohorts captured medications used 1–2 weeks preceding ECG assessment. HCHS/SOL ascertained medications used within four weeks preceding ECG measurement, and the RS captured medication used within 30 days preceding ECG assessment. Participants were classified as thiazide diuretic users if they took a thiazide or thiazide-like diuretic in a single or combination preparation, with or without potassium (K)-sparing agents, and with or without K-supplements.

For cross-sectional studies, the number of exposed participants (N_{exposed}) was defined as the number of participants classified as thiazide users. For studies with longitudinal data, N_{exposed} was calculated as follows:

$$N_{\text{exposed}} = \sum_i \frac{n_i}{1 + (n_i - 1)\hat{\rho}} \frac{\#\{E_{it} = 1\}}{n_i}$$

where n_i is the number of observations for participant i, $\hat{\rho}$ is an estimate of the pairwise visit-to-visit correlation within participants from a Generalized Estimating Equation (GEE)-exchangeable model that does not contain genetic data, and $\#\{E_{it} = 1\}$ is the number of observations for which participant i was exposed.[39]

ECG interval measurement

QT and QRS were digitally recorded by each participating study using resting, supine or semi-recumbent, standard 12-lead ECGs (Supplementary Table 2). Comparable procedures were used for preparing participants, placing electrodes, recording, transmitting, processing, and controlling quality of ECGs. Studies used Marquette MAC 5000, MAC 12, MAC 1200 or MAC PC (GE Healthcare, Milwaukee, Wisconsin, USA), University of Glasgow (Cardiac Science, Manchester, UK), or ACTA (EASOTE, Florence, Italy) machines. Recordings were processed using one of the following programs (Marquette 12SL, MEANS, University of Glasgow, Digital Calipers, or Health 2000 custom-made software. JT was calculated by the formula: JT = QT–QRS.

Genotyping and imputation

Each study conducted genome-wide genotyping independently using either Affymetrix (Santa Clara, CA, USA) or Illumina (San Diego, CA, USA) arrays (Supplementary Table 3). Sex mismatches, duplicate samples, and first-degree relatives (except in ERF, FHS, HCHS/SOL and JHS) were excluded. DNA samples with call rates less than 95–98% were excluded, as were SNPs with SNP call rates less than 90–98%, minor allele frequencies (MAF) less than 1%, or that failed Hardy-Weinberg equilibrium. To maximize genome coverage and comparisons across genotyping platforms, genotypes were imputed using HapMap2,[40–42] 1000 Genomes Phase 1, or 1000 Genomes Phase 3 reference panels.[43,44] Genotypes imputed using build 37 were lifted over to build 36[45,46] to enable comparisons between imputation platforms and results were restricted to SNPs present in HapMap2.

Statistical analyses

Genome-wide pharmacogenomic analyses were performed by each cohort independently across ~2.5 million SNPs for QT, QRS, and JT separately. Drug–SNP interactions were estimated assuming an additive genetic model, using mixed effect models, GEE, or linear regression with robust standard errors. The analytic model varied based on study design and the availability of longitudinal data (Supplementary Table 4). All analyses were adjusted for age (years), sex when applicable, study site or region, principal

Table 1. Study population characteristics of 25 contributing study populations

Population	$N_{exposed}$	N_{total}	*QT in ms, mean (s.d.)*	*QRS in ms, mean (s.d.)*	*JT in ms, mean (s.d.)*	*Age in years, mean (s.d.)*	*Female, %*
European descent							
AGES	435	2256	405 (34)	90 (10)	316 (33)	75 (5)	64.2
ARIC	1449	8567	399 (29)	91 (10)	308 (29)	54 (6)	52.6
CHS	1003	3004	414 (32)	88 (10)	322 (30)	72 (5)	62.5
ERF	29	1792	398 (28)	NA	NA	48 (14)	59.0
FHS	83	3168	415 (30)	88 (10)	328 (30)	40 (9)	52.5
H2000	104	1973	389 (30)	NA	NA	50 (11)	52.0
Health ABC	217	1560	414 (32)	90 (11)	324 (32)	74 (3)	49.4
MESA	453	2216	412 (29)	93 (9)	320 (29)	62 (10)	52.1
NEO	609	5366	406 (29)	93 (10)	313 (29)	56 (6)	47.0
PROSPER	1175	4556	414 (36)	94 (11)	320 (35)	75 (3)	47.0
RS I	523	4805	397 (29)	97 (11)	300 (28)	69 (9)	60.2
RS II	161	1889	403 (28)	98 (11)	305 (28)	65 (8)	56.6
RS III	93	1950	401 (26)	98 (11)	304 (26)	56 (6)	54.1
WHI GARNET[a]	431	1981	401 (29)	86 (9)	315 (29)	66 (7)	100
WHI MOPMAP[a]	268	1383	402 (30)	86 (8)	316 (30)	63 (7)	100
WHI WHIMS[a]	1106	5135	401 (30)	86 (9)	315 (29)	68 (6)	100
Summary	8139	51 601					
African American							
ARIC	916	2169	400 (33)	90 (10)	310 (32)	53 (6)	62.3
CHS	351	666	409 (35)	88 (11)	317 (36)	73 (6)	64.4
Health ABC	268	1151	411 (35)	88 (11)	322 (34)	73 (3)	57.6
JHS	463	1862	410 (32)	92 (10)	319 (30)	50 (12)	60.9
MESA	467	1464	410 (32)	91 (10)	319 (31)	62 (10)	54.4
WHI SHARe	1661	4170	401 (34)	85 (9)	316 (33)	61 (7)	100
Summary	4215	11 482					
Hispanic/Latino							
HCHS/SOL	941	12 024	416 (28)	91 (10)	325 (29)	46 (14)	59.5
MESA	211	1316	409 (30)	91 (10)	318 (30)	61 (10)	51.8
WHI SHARe	224	1776	401 (30)	86 (9)	316 (30)	60 (6)	100
Summary	1376	15 116					

Abbreviations: AGES, Age, Gene/Environment Susceptibility—Reykjavik Study; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; ERF, Erasmus Rucphen Family Study; FHS, Framingham Heart Study; GARNET, Genome-wide Association Research Network into Effects of Treatment; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; Health ABC, Health, Aging, and Body Composition Study; JHS, Jackson Heart Study; JT, JT interval; MESA, Multi-Ethnic Study of Atherosclerosis; MOPMAP, Modification of Particulate Matter-Mediated Arrhythmogenesis in Populations; NEO, the Netherlands Epidemiology of Obesity; $N_{exposed}$, Number of participants exposed to thiazides; N_{total}, Total number of participants in study population after exclusions; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; QRS, QRS interval; QT, QT interval; RS, Rotterdam Study; SHARe, The SNP Health Association Resource; WHI, Women's Health Initiative; WHIMS, the WHI Memory Study. [a]Participants overlapping between GARNET, MOPMAP and WHIMS were excluded from analyses to prevent lack of independence.

components of genetic ancestry, visit-specific RR interval (ms), and visit-specific QT altering medications defined using the University of Arizona Center for Education and Research on Therapeutics (UAZ CERT) QT-prolonging drug classification.[6] Furthermore, ERF, FHS and HCHS/SOL incorporated estimates of relatedness into all analyses. Study-specific results were corrected for genomic inflation (λ).

Previous simulations demonstrated that models using robust standard errors underestimate the variance of coefficient estimates for SNPs with low MAFs.[39] To account for this underestimation, corrected standard errors were calculated using a (Student's) *t*-reference distribution.[39] The degrees of freedom (df) for the *t*-reference distribution were estimated using Satterthwaite's method.[47] When cohorts were unable to implement Satterthwaite's method, an approximate df was calculated as twice the cohort- and SNP-specific product of the SNP imputation quality (range: 0,1), the MAF (range: 0.0,0.50), and $N_{exposed}$. Standard errors were then 'corrected' by assuming a normal reference distribution that yielded the *t*-distribution based *P*-values from the beta estimates.[39] Furthermore, because simulations demonstrated that corrected standard errors were unstable when minor allele counts among the exposed were low, a cohort-specific df filter of 15 was applied across all SNPs.[39]

For each trait, race-stratified and trans-ethnic betas and corrected standard errors were combined with inverse-variance weighted meta-analysis conducted in METAL.[48] We used a genome-wide significance threshold of $P < 5 \times 10^{-8}$ and a suggestive threshold of $P < 5 \times 10^{-6}$. However, the assumptions of a fixed-effects meta-analysis do not always hold between race/ethnicities due to differences in patterns of linkage disequilibrium (LD) across ancestral populations, potential allelic heterogeneity, differences in gene-environment and gene-gene interactions, and differences in environmental and lifestyle factors.[49,50] Therefore, trans-ethnic meta-analysis was also conducted using the Bayesian MANTRA approach and a genome-wide threshold of $\log_{10}(\text{Bayes Factor (BF)}) > 6$ and a suggestive threshold of $\log_{10}(\text{BF}) > 5$.[51] Additionally, previous studies have demonstrated the potential to increase power and detect evidence of pleiotropy by conducting multi-trait analysis across correlated traits.[52,53] To examine potential pleiotropy across ventricular depolarization and repolarization, we conducted cross-phenotype meta-analysis combining *t*-statistics across QRS and JT using an adaptive sum of powered score (aSPU) test, which tests for both concordant and discordant associations across some or all of the included traits.[54] The reference distribution for the aSPU test was calculated using 10^8 simulations.

Genome-wide significant and suggestive meta-analysis results were examined for gene or pathway enrichment. Previous work has shown that it is beneficial to apply multiple methods of gene-set analysis (GSA) when the underlying etiology of the genetic mechanism is unclear.[55–57] We therefore used two methods of GSA. We performed a multiple regression gene analysis approach followed by a self-contained GSA using gene-level regression as implemented in MAGMA.[58] Post-meta-analysis *P*-values were used as input in the analysis and gene-sets were collected from Ingenuity,[59] Panter,[60] KEGG[61] and ConsensusPathDB[62,63] and restricted to biologically motivated pathways involved in the following: ion transport

and homeostasis, transcription and translation, renal and cardiac development and function, and pharmacokinetic/dynamic pathways. Additionally, we selected all SNPs with $P < 1 \times 10^{-5}$ for analysis with DEPICT, which searches for gene, gene-set and tissue enrichment among 14 461 reconstituted gene-sets, eliminating the need to select candidate gene-sets.[64] To account for multiple testing, we applied a false discovery rate (FDR) threshold of 5% for both GSA approaches.

Statistical power simulations

Statistical power to detect drug–SNP interactions using cross-sectional and longitudinal modeling approaches was estimated via simulation studies. Assumptions, which were informed by European ancestry populations, included: (1) 50 000 participants; (2) a two-sided, per-SNP $\alpha = 5 \times 10^{-8}$; (3) a mean heart rate-corrected QT (standard deviation) = 400 (30) ms; (4) $N_{exposed} = 8100$; (5) a mean drug effect for those with zero copies of the minor allele = 5 ms; (6) a mean SNP effect for those not exposed to drug = 0 ms; (7) a MAF = 0.05 or 0.25; (8) an additive model of inheritance; (9) two study visits for longitudinal simulations; (10) within-person QT correlation = 0.80; (11) an attrition rate between visits for longitudinal simulations = 0.13; (12) random missingness rate across study visits = 0.09; and (13) an independent GEE correlation structure for longitudinal simulations. For longitudinal simulations, drug use was either temporally constant or variable. When variable, drug exposure was assumed to be completely random at both visits.

RESULTS

Study characteristics

A total of 78 199 participants were included in the analysis, of which 13 730 (18%) were exposed to thiazides (Table 1). Thiazide use was most common among African Americans (36%), compared with 16% and 9% among European descent and Hispanic/Latino populations, respectively. Mean age ranged from 40 (FHS) to 75 years (PROSPER) and the percentage of females ranged from 47% (NEO, PROSPER) to 100% (WHI). Average QT was between 389 ms (H2000) and 416 ms (HCHS/SOL).

Genome-wide analysis of thiazide–SNP interaction and QT interval

Q-Q plots for individual study results, as well as for meta-analyzed results, demonstrated adequate calibration of study-specific test statistics (Supplementary Figures 1–4). However, the family-based studies (ERF, FHS, HCHS/SOL) showed modest evidence of over-dispersion ($\lambda = 1.07$–1.16).

No genome-wide significant thiazide–SNP interaction effects were detected in any race/ethnic group (Figure 1). However, suggestive interaction effects ($P < 5 \times 10^{-6}$) were found for 22 loci in at least one race/ethnic group: European descent (seven loci), African American (six loci), Hispanic/Latino (six loci), or trans-ethnic (nine loci) (Figure 1; Table 2). Only the *DNAH8/BTBD9* locus was suggestively significant in more than one race/ethnic group (rs862433 in African Americans, rs1950398 in Hispanic/Latinos). Only two of the suggestive SNPs were heterogeneous across populations with $P_{het} < 0.05$ (rs4890550 and rs13223427).

Additionally, examination of 35 loci previously associated with QT in a published main effects GWAS[65] found no significant associations in European descent populations using a Bonferroni corrected threshold of $P < 0.001$ (0.001 = 0.05/35; Supplementary Table 5). The magnitude of the interaction effect was close to zero for all but six of the 35 SNP, which had interaction effects greater than 0.50 ms.

Similarly, while no locus showed genome-wide significance in our trans-ethnic MANTRA analysis (Supplementary Figure 5), one SNP (rs2765279) was above the suggestive threshold, with a $\log_{10}$(BF) of 5.2. Rs2765279, located in *RGSL1*, a gene involved in G-protein signaling regulation, was also the most significant SNP in the fixed-effects trans-ethnic analysis ($P = 3 \times 10^{-7}$).

Genome-wide analysis of thiazide–SNP interaction and QRS interval or JT interval

Results for QRS showed a similar pattern to those for QT (Supplementary Figure 6 and Supplementary Table 6). Whereas no results achieved genome-wide significance, 28 loci showed suggestive evidence of modifying the thiazide-QRS association (four loci in European descent populations, 11 in African Americans, eight in Hispanic/Latinos, and seven in trans-ethnic populations) and only one SNP had a $P_{het} < 0.05$ (rs11591185). The most significant SNP, rs7638855 ($P = 2 \times 10^{-7}$), located upstream from *GAP43*, was also suggestively significant after trans-ethnic analysis in MANTRA ($\log_{10}$(BF) = 5.4; Supplementary Figure 5).

Similarly, no SNPs showed genome-wide significant interaction for JT, although 19 loci were suggestively associated (five loci in European descent populations, four in African Americans, five in Hispanic/Latino, and seven in trans-ethnic populations; Supplementary Figure 6 and Supplementary Table 7). No SNPs showed significant heterogeneity between populations. Moreover, MANTRA analysis identified two SNPs that achieved suggestive significance (Supplementary Figure 5). The rs1264878 variant near *KCNIP4*, a voltage-gated potassium channel interacting protein was the most significant SNP in our fixed-effects meta-analyses ($P = 3 \times 10^{-7}$) and had a $\log_{10}$(BF) = 5.1. However, most significant SNP in MANTRA meta-analyses was rs9303589, in *CA10*, with a $\log_{10}$(BF) = 5.1.

Cross-phenotype meta-analysis

Cross-phenotype meta-analysis found no genome-wide significant evidence of pleiotropy across QRS and JT (Figure 2 and Supplementary Figure 7). However, eight loci had a suggestive evidence of thiazide–SNP interaction after meta-analyzing QRS and JT results (Table 3). These included three loci that were nominally associated with QRS and JT ($P < 0.05$), but whose effects did not reach the suggestive association threshold in either univariate analysis (rs1295230 [*PIK3R6*], rs6931354 [*ADGRB3*] and rs8119517 [*PREX1*]).

Gene and pathway enrichment analysis

Although analysis with DEPICT found no enrichment in a single gene or tissue, gene-set enrichment analysis in European descent populations found enrichment in the *ATXN3* subnetwork for the interactive effect of genotype and thiazide use on QT ($P = 1 \times 10^{-6}$). There was no enrichment found in QRS or JT analyses. MAGMA analyses found significant enrichment in six genes among African Americans in the interactive effect of genotype and thiazide use on QRS: *CNTRL, CPN1, FAM65B, RAB14, ISY1, NELL1* (Supplementary Table 8). No other MAGMA analyses found gene enrichment. MAGMA GSA for QT and JT analyses found significant enrichment for transcription and translational pathways, although no gene-set enrichment was found in QRS analyses (Table 4).

Statistical power

Given the biologic plausibility of the suggestive results for all three traits, we examined statistical power for our analysis to assess our ability to detect interaction effects. Simulations demonstrated that all analyses were underpowered to detect thiazide–SNP interaction effects less than 3 ms (e.g. 15% power to detect an interactive effect of 2 ms; Figure 3). However, even with time-varying drug exposure (that is, observed QT measurement on and off drug within an individual), which demonstrated the greatest power, analyses for SNPs with MAF = 5% did not achieve 80% power until the thiazide–SNP interaction effect reached 6 ms.

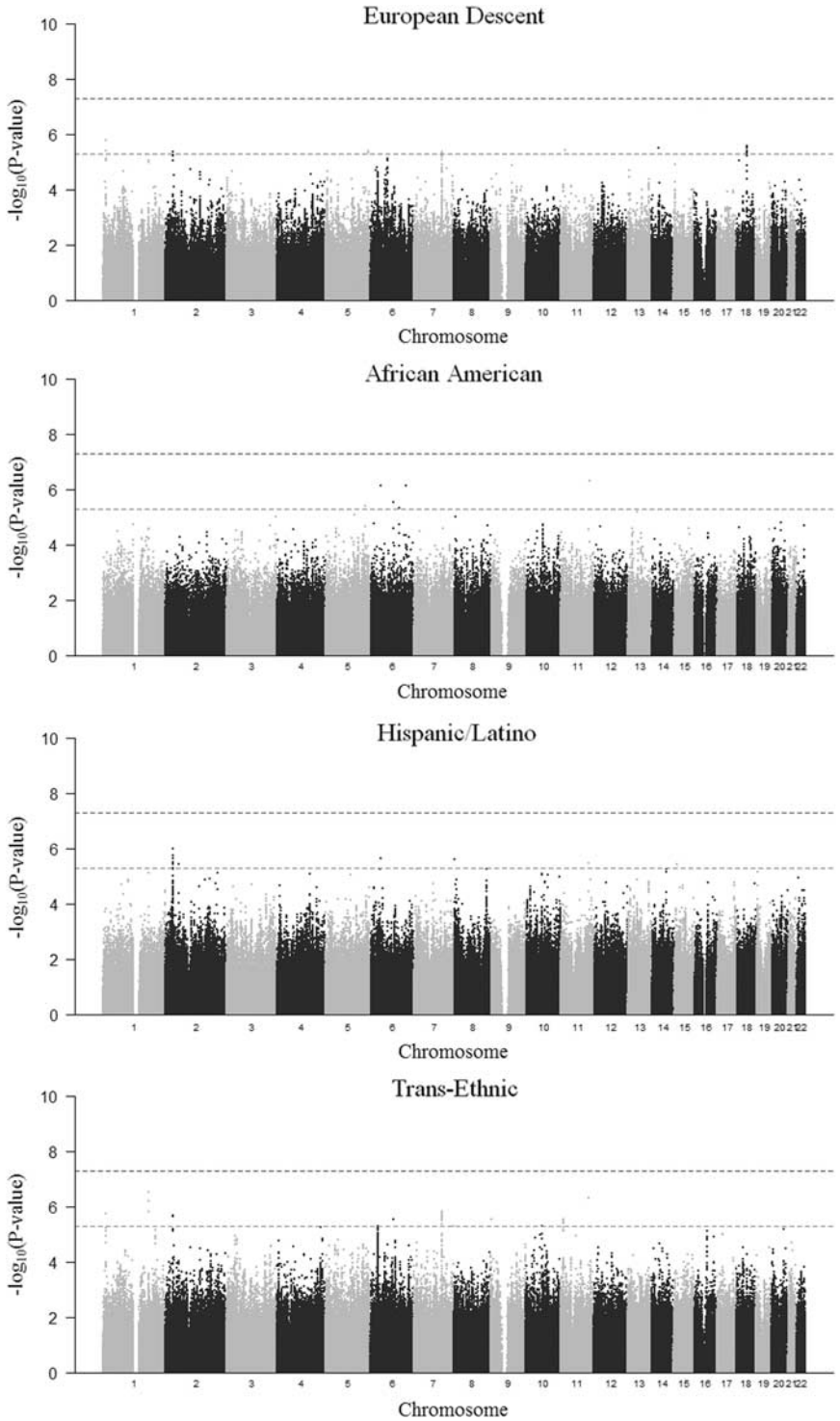

Figure 1. Manhattan plots of *P*-values for thiazide–SNP (single-nucleotide polymorphism) interaction estimates for QT interval analyses after fixed-effects meta-analysis among European descent populations ($N = 51\,601$), African American populations ($N = 11\,482$), Hispanic/Latino populations ($N = 15\,116$), and all populations (trans-ethnic). Each study was analyzed using linear regression, mixed-effects models, or generalized estimating equations and SNPs with a study-specific degree of freedom measure (df = twice the cohort- and SNP-specific product of the SNP imputation quality (range: 0,1), the MAF (range: 0.0,0.50), and the number of individuals exposed to thiazide ($N_{exposed}$)) < 15 were excluded from meta-analysis. The *x*-axis represents the chromosomal position and the *y*-axis represents the $-\log_{10}$(*P*-value). On each plot, genome-wide significance ($P < 5\text{x}10^{-8}$) and suggestive significance ($P < 5\text{x}10^{-6}$) are denoted with dashed lines.

DISCUSSION

In this study, we examined 78 199 participants of European, African American or Hispanic/Latino descent for evidence of thiazide–SNP interactions influencing QT. Although we used a comprehensive approach that considered multi-ethnic populations, leveraged pleiotropy, accommodated population

Table 2. Loci with suggestive evidence of association with the thiazide–SNP interaction effect on QT interval

Locus	*SNP*	*Chr*	*Position*[a]	*CA*	*CAF*	*Interaction effect in ms (s.e.)*	P-*value*	P_{het}
European descent								
KIAA2013	rs17367934	1	11890791	A	0.89	2.4 (0.5)	2×10^{-6}	0.9
SLC14A2	rs4890550	18	41409189	C	0.44	−1.4 (0.3)	3×10^{-6}	0.01
RPS29	rs10143493	14	47999650	A	0.01	−10.6 (2.3)	3×10^{-6}	0.4
NELL1	rs12225793	11	21057283	T	0.12	2.3 (0.5)	4×10^{-6}	1.0
STC2	rs10079004	5	172704698	A	0.71	−1.5 (0.3)	4×10^{-6}	0.4
LCLAT1	rs7608507	2	30447424	A	0.75	1.6 (0.3)	4×10^{-6}	0.7
PPP1R3A	rs13223427	7	113199332	T	0.56	1.4 (0.3)	4×10^{-6}	0.02
African American								
ZBTB16	rs10789991	11	113424299	T	0.03	12.3 (2.4)	5×10^{-7}	0.6
DNAH8	rs862433	6	38968057	A	0.25	−2.6 (0.5)	7×10^{-7}	0.2
Intergenic	rs9376483	6	140352934	T	0.94	7.2 (1.4)	7×10^{-7}	0.5
CASP8AP2	rs7753194	6	90597484	A	0.02	−11.4 (2.4)	3×10^{-6}	0.2
EBF1	rs11135035	5	157833407	A	0.41	2.1 (0.5)	4×10^{-6}	0.9
LAMA4	rs6926485	6	112630302	T	0.64	2.4 (0.5)	5×10^{-6}	0.5
Hispanic/Latino								
SPDYA	rs12475612	2	28883510	T	0.48	−3.5 (0.7)	1×10^{-6}	0.9
BTBD9	rs1950398	6	38666897	T	0.97	9.6 (2.0)	2×10^{-6}	0.05
TDRP	rs6558894	8	480495	C	0.14	−4.9 (1.0)	2×10^{-6}	0.3
COLCA2	rs10749974	11	110696967	A	0.09	−6.0 (1.3)	3×10^{-6}	0.2
CRYGGP	rs17868255	2	51884417	A	0.97	10.3 (2.2)	3×10^{-6}	0.5
RYR3	rs16968694	15	31376213	A	0.18	4.5 (1.0)	3×10^{-6}	1.0
Trans-Ethnic								
RGSL1	rs2765279	1	180693520	T	0.28	1.4 (0.3)	3×10^{-7}	0.4
ZBTB16	rs10789991	11	113424299	T	0.03	12.3 (2.4)	5×10^{-7}	0.6
PPP1R3A	rs17619887	7	113142601	A	0.47	1.2 (0.3)	2×10^{-6}	0.07
KIAA2013	rs17367934	1	11890791	A	0.89	2.3 (0.5)	2×10^{-6}	1.0
LCLAT1	rs6756908	2	30446501	A	0.65	1.3 (0.3)	2×10^{-6}	0.5
FAR1	rs7130476	11	13711632	C	0.90	2.0 (0.4)	3×10^{-6}	0.5
CASP8AP2	rs7753194	6	90597484	A	0.02	−11.4 (2.4)	3×10^{-6}	0.2
SMARCA2	rs1886261	9	2163590	A	0.75	1.5 (0.3)	3×10^{-6}	0.9
ZKSCAN8	rs13205911	6	28232093	T	0.09	−2.5 (0.5)	5×10^{-6}	0.6

Abbreviations: CA, coded allele; CAF, coded allele frequency; Chr, chromosome; P_{het}, *P*-value of heterogeneity; SNP, single-nucleotide polymorphism. [a]Build 36 base-pair position.

heterogeneity, and examined QT as well as its component parts (QRS, JT), we did not identify any genome-wide significant SNPs modifying the association between thiazides and these ECG intervals. However, we identified 74 loci with suggestive evidence of association through either univariate or cross-phenotype analyses as well as evidence of enrichment in pathways involved in transcription and translation.

Interestingly, our suggestive results included multiple loci involved in ion transport and handling, the disruption of which is believed to be an underlying mechanism in drug-induced QT prolongation,[66] supporting the hypothesis that common SNPs modify the thiazide-QT relationship. For example, the *NELL1* locus was previously associated with changes in fasting plasma triglyceride levels in response to hydrochlorothiazide use.[67] Other interesting suggestive results include the *PITX2* and *RYR3* QRS loci identified in Hispanic/Latinos, which may directly regulate ion channel genes and genes involved in calcium handling.[68] Moreover, we found suggestive evidence of thiazide–SNP interactions on QT, QRS, or JT in other genes involved in ion transport and handling, including *STC2*,[69] *EDN1*,[70] *TRPC7*,[71] *PKP2*[72] and *DISC1*,[73] as well as a voltage-gated potassium channel gene (*KCNQ3*).

Despite these intriguing results, our power simulations suggested there was limited power to detect interaction effects of 2 ms, sizes consistent with QT main effects analyses.[65] The low power suggests that larger sample sizes and/or innovative statistical methods may be required to study gene-environment interactions given the stringent genome-wide significance threshold.[74–76] Furthermore, our power simulations demonstrated insufficient power to detect interaction effects of 5 ms or less for less common SNPs (MAF = 5%). Therefore, future work should utilize larger sample sizes, particularly studies with longitudinal data, if available.

Another limitation of our work was that medication use data were collected infrequently, e.g. years apart. Particularly, medication assessments covered only one to two weeks of medication use in most participating cohorts and variables such as medication dosage and duration of use were not available universally across studies. Previous work has demonstrated a dose-dependent relationship between thiazide use and cardiac arrest, a potential outcome of QT prolongation.[77] However, we were unable to identify participants using high dose thiazides because medication dosage data was unavailable in all cohorts. Furthermore, K^+ measurements and information on K^+ supplements was not obtained across all cohorts so we were unable to adjust for K^+ levels in our analyses, despite the known role of thiazide diuretics in inducing hypokalemia and the role of hypokalemia in causing QT prolongation.[78,79]

Furthermore, ECG intervals are known to vary in the presence of cardiovascular disease (CVD).[80] While we did exclude participants with certain types of CVD including prevalent heart failure and atrial fibrillation, we were not able to further characterize the role

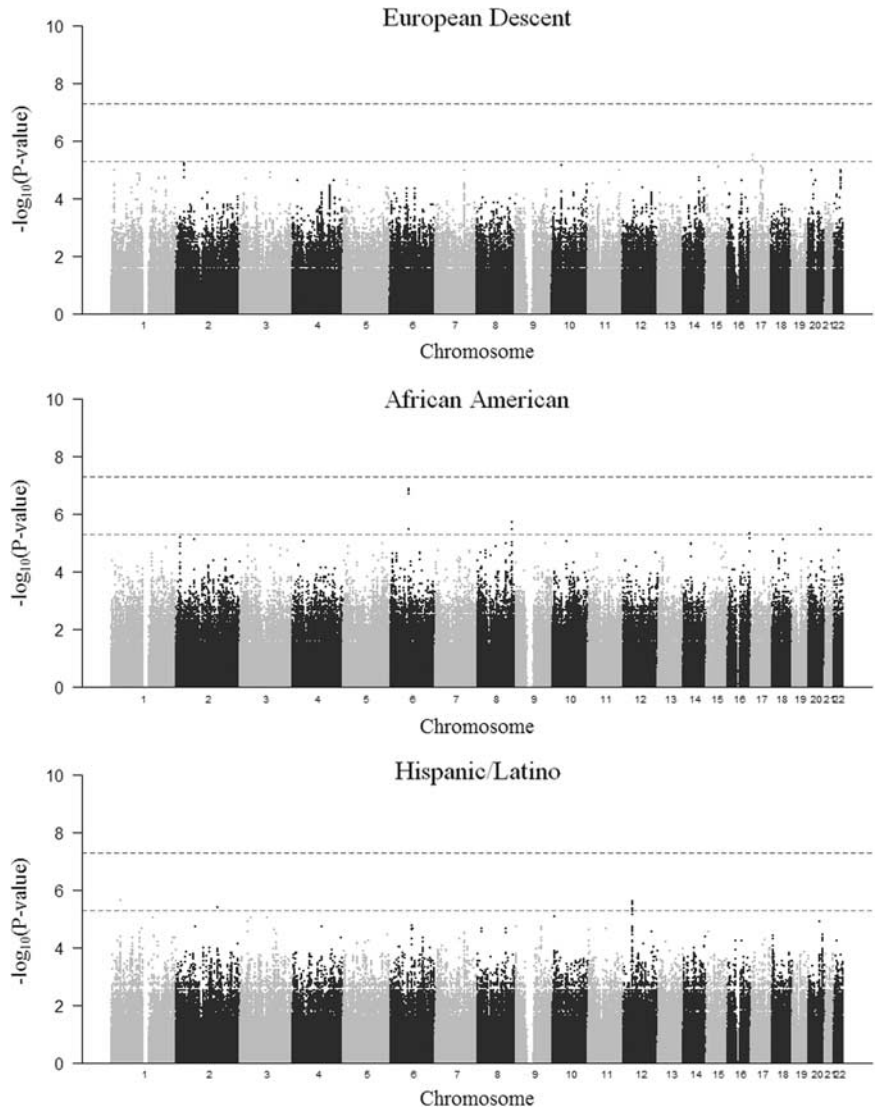

Figure 2. Manhattan plots of *P*-values thiazide–SNP interaction estimates after cross-phenotype meta-analysis (QRS interval, JT interval) using aSPU among European descent populations ($N = 47\,836$), African American populations ($N = 11\,482$), and Hispanic/Latino populations (15 116). For each trait separately, each study was analyzed using linear regression, mixed-effects models, or generalized estimating equations and SNPs with a study-specific degree of freedom measure (df = twice the cohort- and SNP-specific product of the SNP imputation quality (range: 0,1), the MAF (range: 0.0,0.50), and the number of individuals exposed to thiazide ($N_{exposed}$)) < 15 were excluded from cross-phenotype meta-analysis. The *x*-axis represents the chromosomal position and the *y*-axis represents the $-\log_{10}$(*P*-value). On each plot, genome-wide significance ($P < 5x10^{-8}$) and suggestive significance ($P < 5x10^{-6}$) are denoted with dashed lines.

of CVD in the pharmacogenomics of thiazide use and QT duration. Given that we saw larger mean QT and JT intervals in Hispanic/Latino populations than in European descent or African American populations in our study sample, as well a substantial difference in mean exposure to thiazides, ranging from just 9% in Hispanic/Latinos to 37% in African Americans, our analyses are limited by the heterogeneity of exposure and outcome in our population. The large difference in thiazide exposure between race/ethnic groups could also indicate an underlying difference in CVD prevalence among our populations. Considering that pharmacogenomic studies such as this one are already limited in their power to detect effects, the addition of unmeasured heterogeneity such as CVD status could further reduce our power to detect genetic effects modifying the relationship between thiazides and QT. Therefore, future work should consider alternate study designs, such as clinical trials or specially collected cohorts, as settings for pharmacogenomics work. In clinical trials or specialty cohorts, populations can be more closely controlled and therefore more homogeneous in traits that may confound the relationship between thiazides and QT.

Additionally, observational cohort studies are known to be susceptible to selection biases, such as prevalent user bias, whereby long-term medication users are least likely to suffer from ADRs and users with ADRs often stop therapy and therefore have a lower chance of being seen while on therapy.[81,82] Unfortunately, without information on duration of use, it is difficult to evaluate the effect of prevalent user bias on study results. Indeed, it is unclear if these biases are of concern in pharmacogenomic studies.[83,84] Additional work is needed to assess whether selection bias requires more consideration in pharmacogenomic research and to assess possible advantages of alternative designs, such as active comparator designs (whereby the control group contains participants using a different class of medications with similar indications to the medication of interest) or new user

Table 3. Loci with suggestive evidence modifying the effect of Thiazide on QRS and JT intervals after cross-phenotype meta-analysis

Locus	*SNP*	*Chr*	*Position*[a]	*CA*	*CAF*	P-*value*	*Univariate* P-*value*	
							QRS	*JT*
European descent								
PIK3R6	rs1295230	17	8682305	T	0.02	3×10^{-6}	0.008	0.001
African American								
ADGRB3	rs6931354	6	69527128	A	0.21	1×10^{-7}	0.005	0.0002
ADCY8	rs10108730	8	131767803	T	0.79	2×10^{-6}	1×10^{-5}	0.0003
PREX1	rs8119517	20	46464282	A	0.94	3×10^{-6}	0.0005	0.02
CDH13	rs11649358	16	81415652	A	0.75	5×10^{-6}	$9x10^{-6}$	0.001
Hispanic/Latino								
AK2	rs11591185	1	33274771	A	0.07	2×10^{-6}	7×10^{-7}	3×10^{-5}
ASS1P14	rs12578228	12	33030528	T	0.10	2×10^{-6}	2×10^{-6}	2×10^{-5}
GALNT13	rs17553946	2	155055407	A	0.23	4×10^{-6}	0.005	9×10^{-7}

Abbreviations: CA, coded allele; CAF, coded allele frequency; Chr, chromosome; JT, JT interval; QRS, QRS interval; SNP, single-nucleotide polymorphism. [a]Build 36 base-pair position.

Table 4. Gene-sets with enrichment for genotype–thiazide interaction effects

Trait	*Population*	*Gene-set*	P-*value*	*FDR*
QT	Hispanic/Latino	Nucleotide Binding	5×10^{-6}	0.004
		Metal Ion Binding	6×10^{-6}	0.004
		tRNA Adenine-N1 Methyltransferase Activity	6×10^{-5}	0.03
		Transcription Coactivator Activity	8×10^{-5}	0.03
		Transcriptional Activity of SMAD2, SMAD3, SMAD4, Heterotrimer	0.0001	0.03
		Zinc Ion Binding	0.0002	0.04
		Other RNA Binding Protein	0.0002	0.04
		Insulin-like Growth Factor-2 mRNA Binding Proteins (IGF2BPS/IMPS/VICKZS)	0.0003	0.05
	Trans-Ethnic	General RNA Polymerase II Transcription	4×10^{-6}	0.006
		Transcription	4×10^{-5}	0.03
JT	African American	Transcription Factor TFIID Complex	7×10^{-5}	0.05
		Aminoacyl-tRNA Synthetase Multienzyme Complex	0.0001	0.05
		tRNA Aminoacylation for Protein Translation	0.0001	0.05
		Transcription Factor TFTC Complex	0.0001	0.05
	Trans-Ethnic	Transciption	3×10^{-5}	0.03
		General RNA Polymerase II Transcription Factor Activity	4×10^{-5}	0.03

Abbreviations: FDR, false discovery rate; JT, JT interval; QT, QT interval.

designs (whereby prevalent users are excluded). Moreover, medication inventories may be associated with non-negligible measurement error. For example, while Smith *et al.* reported good agreement between thiazide use measured using medication inventories and serum thiazide measurements, specificity remained moderate.[85]

Given the challenges associated with assembling an adequately powered pharmacogenomics study, electronic medical records (EMRs) represent a potential untapped resource that may merit evaluation. Strengths of EMRs include the potential to provide a more complete medication history, which could enable sensitivity analyses examining variables such as medication dose and duration of use. Furthermore, consortia such as eMERGE have demonstrated the feasibility of linking EMRs to genetic data for use in genetic research,[86] and have successfully identified genetic variants modifying drug response.[87] However, EMRs have limitations. Investigators using EMR data cannot control participant recruitment, timing and accuracy of data collection, or population representativeness.[88] Considering ECG research specifically, cohort studies administer ECGs to all participants at study visits, whereas EMRs may capture ECGs for patients with medical indications, providing an inherently different population. EMRs therefore have the potential to greatly advance pharmacogenomic research but warrant further evaluation.

In conclusion, our findings suggest that additional work is needed to fully elucidate potential pharmacogenomic effects influencing the thiazide-QT relationship. Our suggestive results support a possible role of genetics in modifying the association between thiazides and QT. However, these findings can inform the biology of thiazide-induced QT prolongation and do not preclude the possibility of common variants with small effects or rare variants with larger effects. Future work that leverages larger sample sizes, such as those available in EMRs, and innovative statistical methods to validate these suggestive findings is needed. The FDA considers further regulation of drugs that prolong QT by as little as 5 ms, a small increment easily achieved by the combination of genetic and pharmaceutical effects,[37,89] making it critical that we unravel the complex etiology of drug-induced QT prolongation.[90] Pharmacogenomics remain a promising avenue for understanding variability in drug

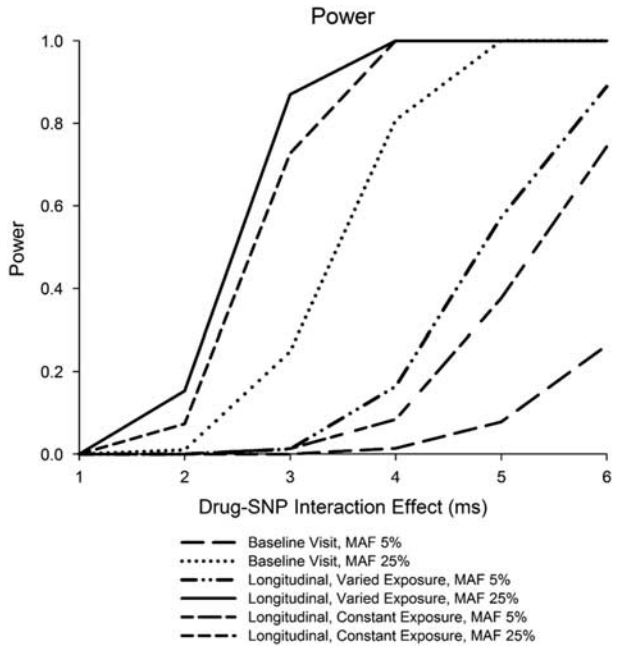

Figure 3. Statistical power of a simulated pharmacogenomics study of QT. The *x*-axis represents the range of tested drug–SNP interaction effects in milliseconds (ms). The *y*-axis represents the power to detect the tested drug–SNP interaction effect. The following assumptions were used for the calculations: 2 serial visits measuring electrocardiograms (ECGs) and drug exposure, $N = 50\,000$ participants, a single-nucleotide polymorphism (SNP) minor allele frequency (MAF) of 5% or 25%, and the $N_{exposed} = 8100$. Simulation analyses were run using only the baseline visit (cross-sectional) and a longitudinal model. Under the longitudinal model, simulations were run with all participants having constant drug exposure across visits or having varied drug exposure across visits. Cross-sectional models were run using linear regression and longitudinal models were run using a generalized estimating equation with an independence working correlation.

response and for utilizing genetics to improve public health but innovative solutions are needed to overcome inherent challenges.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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